TENT COOPERATION TRE. /

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 23 October 2000 (23.10.00)	
International application No. PCT/US00/04270	**Applicant's or agent's file reference** DLF-002.1PCT
International filing date (day/month/year) 18 February 2000 (18.02.00)	**Priority date** (day/month/year) 18 February 1999 (18.02.99)
Applicant FAUSTMAN, Denise, L.	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

11 September 2000 (11.09.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Christelle Croci
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

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WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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A01N 1/00, 1/02

A1

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(63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application
US 09/252,331 (CIP)
Filed on 18 February 1999 (18.02.99)

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(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: METHOD FOR INHIBITING TRANSPLANT REJECTION

(57) Abstract

A method for inhibiting rejection of tissues transplanted into a mammalian host is disclosed. Treatment of the tissues with an enzyme or combination of enzyme, particularly papain, to eliminate cell surface structures necessary for recognition by the host's immune system, particularly MHC Class I molecules, avoids or reduces the attack of the host's immune system on the transplanted tissues. Tissues that are enzymatically shaved of MHC Class I antigens and/or other critical adhesion molecules can be rendered at least temporarily resistant or immune to attack by cytolytic T lymphocytes, helper T lymphocytes, antibodies, or other effector cells of a host's immune system, thereby enhancing the survivability of the tissues in the host after transplant.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/04270

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : A01N 1/00, 1/02
US CL :424/94.2; 435/1.1, 2
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 424/94.2; 435/1.1, 2

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
WEST USPT, DWPI; STN MEDLINE, BIOSIS, CA
search terms: transplantation, donor tissue, MHC Class I antigens, papan, galactosidase

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X ---- Y	**GALATI** et al. Quantative Cytometry of MHC Class I Digestion from Living Cells. Cytometry. 1997. Vol 27, pages 77-83.	15,19, 22-25,27, 29,30,33 ---------- 1-14,16-18, 21,26,28, 31,32,34-37
X ---- Y	US 5,416,260 A (**KOLLER** et al) 16 May 1995. abstract.	24 ---------- 1-23,27-37
X ---- Y	US 4,399,123 A (**OLIVER** et al) 16 August 1983. col. 6-7, examples 1-4; col. 2, lines 16, 37-45, 60-65.	1-8,15-21 ---------- 9-14,22-37

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search
02 JUNE 2000

Date of mailing of the international search report
15 JUN 2000

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Authorized officer
VERA AFREMOVA
Telephone No. (703) 308-0196

Form PCT/ISA/210 (second sheet) (July 1998)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/04270

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	**STONE** et al. Porcine Cartilage Transplants in the Cynomolgus Monkey.III. Transplantation of alpha-Galactosidase-Treated Porcine Cartilage. Transplantation. 27 June 1998. Vol 65. No. 12, pages 1577-1583, abstract.	1-37

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To: LEON R. YANKWICH
YANKWICH & ASSOCIATES
150 BISHOP ALLEN DRIVE
CAMBRIDGE MA 02139

PCT

NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of Mailing *(day/month/year)*	09 AUG 2001
Applicant's or agent's file reference: DLF-002.1PCT	IMPORTANT NOTIFICATION

International application No.	International filing date *(day/month/year)*	Priority Date *(day/month/year)*
PCT/US00/04270	18 FEBRUARY 2000	18 FEBRUARY 1999

Applicant
FAUSTMAN, DENISE L.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/US	Authorized officer
Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	VERA AFREMOVA
Facsimile No. (703) 305-3230	Telephone No. (703) 308-0196

Form PCT/IPEA/416 (July 1992)*

09/913664

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference DLF-002.1PCT	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US00/04270	International filing date *(day/month/year)* 18 FEBRUARY 2000	Priority date *(day/month/year)* 18 FEBRUARY 1999
International Patent Classification (IPC) or national classification and IPC IPC(7): A01N 1/00, 1/02 and US Cl.: 424/94.2; 435/1.1, 2		
Applicant FAUSTMAN, DENISE L.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets.

   [X] This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 4 sheets.

3. This report contains indications relating to the following items:

   - I [X] Basis of the report
   - II [ ] Priority
   - III [ ] Non-establishment of report with regard to novelty, inventive step or industrial applicability
   - IV [ ] Lack of unity of invention
   - V [X] Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI [ ] Certain documents cited
   - VII [ ] Certain defects in the international application
   - VIII [ ] Certain observations on the international application

Date of submission of the demand	Date of completion of this report
11 SEPTEMBER 2000	29 MAY 2001
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer VERA EFREMOVA Telephone No. (703) 308-0196

Form PCT/IPEA/409 (cover sheet) (July 1998)*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US00/04270

I. Basis of the report

1. With regard to the elements of the international application:*

☐ the international application as originally filed

☒ the description:
pages (See Attached) , as originally filed
pages _____ , filed with the demand
pages _____ , filed with the letter of _____

☒ the claims:
pages (See Attached) , as originally filed
pages _____ , as amended (together with any statement) under Article 19
pages _____ , filed with the demand
pages _____ , filed with the letter of _____

☒ the drawings:
pages (See Attached) , as originally filed
pages _____ , filed with the demand
pages _____ , filed with the letter of _____

☒ the sequence listing part of the description:
pages (See Attached) , as originally filed
pages _____ , filed with the demand
pages _____ , filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in printed form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the writen sequence listing has been furnished.

4. ☒ The amendments have resulted in the cancellation of:

☒ the description, pages NONE

☒ the claims, Nos. NONE

☒ the drawings, sheets/~~fig~~ NONE

5. ☐ This report has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

***Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. statement

Novelty (N)	Claims	(Please See supplemental sheet)	YES
	Claims	(Please See supplemental sheet)	NO
Inventive Step (IS)	Claims	(Please See supplemental sheet)	YES
	Claims	(Please See supplemental sheet)	NO
Industrial Applicability (IA)	Claims	(Please See supplemental sheet)	YES
	Claims	(Please See supplemental sheet)	NO

2. citations and explanations (Rule 70.7)

Claims 15, 19, 22-25, 27, 29, 30 and 33 lack novelty under PCT Article 33(2) as being anticipated by Galati et al..

The claims are directed to a method for treating mammal donor tissue or for inhibiting rejection of mammal donor tissue wherein the method comprises a step of treating a mammal donor tissue with an enzyme effective for removing or temporarily ablating MHC Class I antigens from the donor tissue. Some claims are/are further drawn to the use of enzyme such as papain. Some claims are further drawn to the use of a solution with papain at 5-60 mg/ml for a period of 5 minutes to 24 hours. Some claims are further drawn to treatment of blood cells. Some claims are directed to a mammalian tissue treated with papain. Some claims are directed to a transplantation pack comprising tissue in a nutrient or preservative solution and a papain.

Galati et al. discloses a method for removing MHC Class I antigens by treating various living tissue cells with a solution of papain at 0.5-4 mg/ml for 2-6 hours. Digestion or removal of MHC Class I molecules were carried on living cells. See abstract and page 78 at "Materials and Methods" section. The mammalian tissue cells treated with papain were viable and they had a significant reduction of MHC class I antigenic molecules (page 79 at "Results" section). Thus, the method and tissue as claimed are considered to be anticipated by the cited method and tissue. Although the cited reference does not clearly teach a whole composition as a transplantation pack, the cited composition comprises identical items as claimed such as mammalian tissues or cell lines and an enzyme effective for removing MHC Class I antigen or papain. Thus, the claimed invention is anticipated by the cited reference.

Claims 1-8 lack novelty under PCT Article 33(2)as being anticipated by US 4,399,123.

The claims are directed to a method for inhibiting rejection of mammal donor tissue wherein the method comprises a step of treating a mammal donor tissue with an enzyme effective for removing MHC Class I antigen and step of transplanting the treated tissue. Some claims are further drawn to the use of a (Continued on Supplemental Sheet.)

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

I. BASIS OF REPORT:

This report has been drawn on the basis of the description,
page(s) 1-13, as originally filed.
page(s) NONE, filed with the demand.
and additional amendments:
NONE

This report has been drawn on the basis of the claims,
page(s) none, as originally filed.
page(s) NONE, as amended under Article 19.
page(s) NONE, filed with the demand.
and additional amendments:
Pages 14-17, filed with the letter of 07 May 2001.

This report has been drawn on the basis of the drawings,
page(s) NONE, as originally filed.
page(s) NONE, filed with the demand.
and additional amendments:
NONE

This report has been drawn on the basis of the sequence listing part of the description:
page(s) NONE, as originally filed.
pages(s) NONE, filed with the demand.
and additional amendments:
NONE

V. 1. REASONED STATEMENTS:
The report as to Novelty was positive (YES) with respect to claims 9-14,16-18,20,21,26,28,31,32,34-37.
The report as to Novelty was negative (NO) with respect to claims 1-8,15,19,22-25,27,29,30,33.
The report as to Inventive Step was positive (YES) with respect to claims NONE.
The report as to Inventive Step was negative (NO) with respect to claims 1-37.
The report as to Industrial Applicability was positive (YES) with respect to claims 1-37.
The report as to Industrial Applicability was negative (NO) with respect to claims NONE.

V. 2. REASONED STATEMENTS - CITATIONS AND EXPLANATIONS (Continued):
second enzyme to remove antigenic surface structure. Some claims are further drawn to the treatment of skin cells.

US 4,399,123 teaches a method for inhibiting rejection of donor tissue wherein the method comprises a step of treating a mammalian fibrous tissues with a first proteolytic enzyme and a second carbohydrate splitting enzyme in order to remove antigenic structures and to obtain a preparation which is intended and suitable for homo- and hetero-transplantation (abstract or col. 2, lines 1-45). The preferred enzyme combinations are trypsin or chymotrypsin and amylase (examples 1-4). The suitable proteolytic enzymes include papain (col. 2, lines 63-64). The fibrous tissues are human or porcine dermis tissues. Thus, the cited method comprises identical active step and identical structural elements as the claimed method. Although the cited reference does not clearly demonstrate the removal of MHC Class I antigenic molecules, the cited method is reasonably expected to result in the removal of glycoproteins such as MHC Class I molecules particularly in view that two identical types of enzymes such as proteolytic and carbohydrate splitting enzymes are used for removal of antigenic structures including glycoproteins (col.2, line 16).

Claims 1-34 lack an inventive step under PCT Article 33(3) as being obvious over US 4,399,123 taken with Galati et al., US 5,416,260 and Stone et al.

The claims are directed to a method for preparing donor tissues for transplantation or for inhibiting rejection of mammalian donor tissue wherein the method comprises a step of treating a donor tissue with a combination of two enzymes such as an enzyme effective for removing MHC Class I antigen from the donor tissue or papain and a second enzyme such as galactosidase. Some claims are further drawn to the use of a solution with papain at 5-60 mg/ml for a period of 5 minutes to 24 hours. Some claims are further drawn to the treatment of blood cells, skin cells, etc. Some claims are directed to a mammalian tissue with a reduced amounts of MHC Class I antigens. Some claims are directed to a transplantation pack comprising tissue

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

in a nutrient or preservative solution and a papain.

US 4,399,123 is applied here for the disclosure of a mammalian tissues obtained by a method and for the disclosure of a method for inhibiting rejection of a donor tissue wherein the method comprises a step of treating a tissue with two types of enzymes in order to remove antigenic structures including glycoproteins and polysaccharides. The reference is lacking a particular exemplified disclosure of a proteolytic enzyme such as papain in a combination with a particular carbohydrate splitting enzyme such as galactosidase. However, the cited patent suggests the use of papain as a suitable proteolytic enzyme. And the other reference by Galati et al. particularly demonstrates that papain removes glycoproteins such as MHC Class I molecules carried out on living mammalian cells in a method for inhibiting rejection of donor tissue or a method for reducing amounts of antigenic molecules recognizable by lymphocytes.

The reference by Stone et al. discloses tissues for transplantation and a method for inhibiting rejection of a donor tissue by treating the tissue with galactosidase (pages 1577-1578 at paragraphs "Methods" and "Conclusions").

And US 5,416,260 teaches that tissues lacking MHC antigens are universal donor cells for transplantation which would not be rejected or destroyed by recipient immune system (col. 1, lines 15-18, 40-55; col. 4, lines 15-21). Although the cited patent discloses tissue which is obtained by recombinant techniques rather than enzymatic treatment, the cited patent clearly suggests the various tissues/cells with reduced or eliminated amounts of MHC Class I antigens as suitable for transplantation.

Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to substitute papain and galactosidase for particular enzymes in the method for preparing donor tissues as disclosed by US 4,399,123 with a reasonable expectation of success in practicing method for inhibiting rejection of donor tissues and obtaining tissues suitable for transplantation because the use of papain have been suggested [US 4,399,123] and/or shown [Galati et al.] by the cited prior art references and removal of gal-epitopes with galactosidase have been successfully demonstrated for transplants [Stone et al.]. Since the use of cells lacking MHC Class I antigens as universal donor tissues [US 5,416,260] and methods for obtaining such tissues are known in the art of cellular and organ therapies including transplantation [US 4,399,123; Galati et al.; Stone et al.] the claimed invention as a whole was clearly lacking an inventive step particularly in the absence of evidence to the contrary.

With regard to the claimed invention directed to a transplantation pack it is noted that although this composition is not clearly disclosed by the cited US patent '123, the similar composition intended for transplantation comprising the similar items as claimed such as donor tissues and combination of two types of enzymes, is suggested by the cited US patent '123 and, thus, a transplantation pack would have been obvious to those of ordinary skill in the art within the meaning of the lack of an inventive step under PCT Article 33(3).

With regard to the claims directed to mammalian transplant tissues it is noted the mammalian tissue as disclosed by US 4,399,123 and Galati et al. appear to be similar to the presently claimed tissue. The disclosed donor tissues have been treated with two types of enzymes and they are viable and suitable for transplantation. Even if the claimed tissues are not identical to the referenced tissue with regard to some undisclosed characteristics such as, for example, particular amounts of particular molecules removed, the differences between that which is disclosed and that which is claimed are considered to be so slight that the referenced tissues are likely inherently possess the same characteristics of the claimed tissues particularly in view of the similar characteristics which they have been shown to share with regard to reduction of antigenic surface molecules, viability and/or successful transplantation. And, thus, they would have been obvious to those of ordinary skill in the art within the meaning of the lack of an inventive step under PCT Article 33(3).

Applicants' amendment to the claims is drawn to emphasize a temporary effect of an enzymatic removal of MHC antigens from the surface of tissues/cells intended for transplantation. Thus, the claim objection for lacking novelty under PCT Article 33(2) as being anticipated by US 5,416,260 has been withdrawn since the disclosed recombinant preparation of tissues lacking MHC antigens would result in permanent removal of MHC antigens without possibility for future expression.
However, with regard to the other cited references applicants amendment and arguments are not persuasive because enzymatic removal of MHC antigens have been demonstrated in the prior art and tissues lacking MHC antigens have been taught as universal donor for transplantation. The reference by Galati et al. discloses removal of MHC antigens from living cells or tissues and, thus, these treated tissues/cells are reasonably believed to be capable of future expression of MHC as intended or as argued by applicants. With regard to the cited patent US 4,399,123 applicants seem to argue that it suggests for transplantation a tissue lacking MHC antigens which is dead or sterilized. This is not found true because sterilization which is described by US'123 is intended for purification from contamination rather than preparation of a dead tissue (col. 5, line 48 or line 66). Moreover, the cited patent teaches do not exceed certain limits in application of a sterilizing agent such as glutaraldehyde solution, for example: col.6, lines 2-3.

---------- NEW CITATIONS ----------
NONE

TENT COOPERATION TRE /

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING
AMENDMENTS OF THE CLAIMS

(PCT Rule 62 and
Administrative Instructions, Section 417)

To:

Assistant Commissioner for Patents
United States Patent and Trademark
Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as International Preliminary Examining Authority

Date of mailing (day/month/year)	
23 October 2000 (23.10.00)	
International application No.	International filing date (day/month/year)
PCT/US00/04270	18 February 2000 (18.02.00)
Applicant	
FAUSTMAN, Denise, L.	

The International Bureau hereby informs the International Preliminary Examining Authority that no amendments under Article 19 have been received by the International Bureau (Administrative Instructions, Section 417).

The International Bureau of WIPO
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1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer

Christelle Croci

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